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CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,  
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
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(71) Applicant (*for all designated States except US*): BAYER  
HEALTHCARE AG [DE/DE]; 51368 Leverkusen (DE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): SCHWERS,  
Stephan [DE/DE]; Düsseldorf Str. 35, 51145 Köln  
(DE). KALLABIS, Harald [DE/DE]; Wolfskaul 8, 51061  
Köln (DE). STROPP, Udo [DE/DE]; Suitbertusweg 8,  
42781 Haan (DE).

(74) Common Representative: BAYER HEALTHCARE  
AG; Law and Patents, Patents and Licensing, 51368  
Leverkusen (DE).

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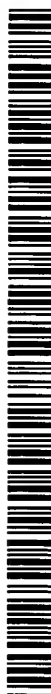
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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: SINGLE NUCLEOTIDE POLYMORPHISMS PREDICTING ADVERSE DRUG REACTIONS AND DRUG EFFI-  
CACY IN CARDIOVASCULAR DISEASE

(57) Abstract: The invention provides diagnostic methods and kits including oligo and/or polynucleotides or derivatives, including as well antibodies determining whether a human subject is at risk of getting adverse drug reaction after statin therapy or whether the human subject is a high or low responder or a good or bad metabolizer of statins. The invention provides further diagnostic methods and kits including antibodies determining whether a human subject is at risk for a cardiovascular disease. Still further the invention provides polymorphic sequences and other genes. The present invention further relates to isolated polynucleotides encoding a phenotype associated (PA) gene polypeptide useful in methods to identify therapeutic agents and useful for preparation of a medicament to treat cardiovascular disease or influence drug response, the polynucleotide is selected from the group comprising: SEQ ID 1-168 with allelic variation as indicated in the sequences section contained in a functional surrounding like full length cDNA for PA gene polypeptide and with or without the PA gene promoter sequence.



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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09126

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 G01N33/50 C07K14/47 C12N15/63 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q G01N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, Sequence Search, MEDLINE, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	<p>BASSO FEDERICA ET AL: "Interleukin-6 -174G&gt;C polymorphism and risk of coronary heart disease in West of Scotland Coronary Prevention Study (WOSCOPS)." ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY, vol. 22, no. 4, April 2002 (2002-04), pages 599-604, XP002241155 April, 2002 ISSN: 1079-5642 the whole document</p> <p style="text-align: center;">----- -/--</p>	1-16
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Gabriels, J

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09126

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PEDRO-BOTET JUAN ET AL: "Apolipoprotein E genotype affects plasma lipid response to atorvastatin in a gender specific manner." ATHEROSCLEROSIS, vol. 158, no. 1, September 2001 (2001-09), pages 183-193, XP002241156 ISSN: 0021-9150 the whole document</p> <p style="text-align: center;">-----</p>	1-16
X	<p>TURNER STEPHEN T ET AL: "Antihypertensive pharmacogenetics: Getting the right drug into the right patient." JOURNAL OF HYPERTENSION, vol. 19, no. 1, January 2001 (2001-01), pages 1-11, XP002241062 ISSN: 0263-6352 the whole document</p> <p style="text-align: center;">-----</p>	1-16
X	<p>PIRMOHAMED M ET AL: "Genetic susceptibility to adverse drug reactions" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, vol. 22, no. 6, 1 June 2001 (2001-06-01), pages 298-305, XP004241902 ISSN: 0165-6147 the whole document</p> <p style="text-align: center;">-----</p>	1-16
X	<p>WO 99/02735 A (MILLENNIUM PHARM INC ;TRUSTEES OF TUFTS UNIVERSITY (US)) 21 January 1999 (1999-01-21) page 63, line 17 - page 64, line 20; claim 1</p> <p style="text-align: center;">-----</p>	1-16
X	<p>WO 02/059369 A (UNIV MEDICINE AND DENTISTRY) 1 August 2002 (2002-08-01) claims 1-25</p> <p style="text-align: center;">-----</p>	1-16
X	<p>WO 00/79003 A (ASTRAZENECA UK LTD) 28 December 2000 (2000-12-28) claims 1-11</p> <p style="text-align: center;">-----</p>	1-16
X	<p>WO 00/22166 A (EURONA MEDICAL AB ;NORBERG LEIF TORBJORN (SE); JONSSON LENA (SE);) 20 April 2000 (2000-04-20) claims 1-16</p> <p style="text-align: center;">-----</p>	1-16
X	<p>WO 99/14363 A (EURONA MEDICAL AB ;KARPE FREDRIK (SE)) 25 March 1999 (1999-03-25) claims 1-11</p> <p style="text-align: center;">-----</p>	1-16
X	<p>WO 98/45477 A (EURONA MEDICAL AB ;LINDSTROEM PER HARRY RUTGER (SE); ANDERSSON MAR) 15 October 1998 (1998-10-15) claims 1-8</p> <p style="text-align: center;">-----</p>	1-16

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/09126

## **Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: **8,10**  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## **Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

**see additional sheet**

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Invention 1: claims 1-16 (all partially)**

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-16 (all partially)

An isolated polynucleotide according to SEQ ID NO:1, a polypeptide encoded thereby, an expression vector therefore, a host cell containing this vector, a pharmaceutical composition containing said vector, and methods using these components for producing the polypeptide encoded by SEQ ID NO:1, for determining the risk for cardiovascular disease, for screening for modulators of SEQ ID NO:1, for determining the response to therapy. Uses and kits thereof.

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Invention 2-168: claims 1-16 (all partially)

Idem for invention 2 to 168 but limited to SEQ ID NO:2-168 (Invention 2 = SEQ ID NO:2, ..., Invention 168 = SEQ ID NO:168).

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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Continuation of Box I.2

Claims Nos.: 8,10

Present claims 8, 9, and 10 relate to reagents that modulate the activity of a PA polypeptide identified by the method of claim 7.

The claims cover all reagents having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for none of such reagents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the reagents by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 8 and 10 and claim 9 has been searched with respect to the expression vector of claim 2.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/09126

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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